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Total Number of Pages in This Submission

Application Number	**09/544,910**
Filing Date	**April 7, 2000**
First Named Inventor	**HUANG, YADONG**
Group Art Unit	**1642**
Examiner Name	**RAWLINGS, STEPHEN L.**
Attorney Docket Number	**UCAL-121**

ENCLOSURES (check all that apply)

- [X] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Documents
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] After Allowance Communication to Group
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  1) **Appellants' Brief (IN TRIPLICATE)**
  2) **Return Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**PAULA A. BORDEN, 42,344** **BOZICEVIC, FIELD & FRANCIS LLP**
Signature	
Date	**April 25, 2003**

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 160.00

Complete if Known	
Application Number	09/544,910
Filing Date	April 7, 2000
First Named Inventor	HUANG, YADONG
Examiner Name	RAWLINGS, STEPHEN L.
Art Unit	1642
Attorney Docket No.	UCAL-121

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

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Deposit Account Name **Bozicevic, Field & Francis LLP**

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims	Fee from below	Fee Paid
Total Claims	-20** =	x	=
Indep. Claims	-3** =	x	=
Multiple Dependent			=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) $ 0.00

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examination action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	160.00
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,300	2453	650	Petition to revive – unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

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SUBMITTED BY					
Name (Print/Type)	Paula A. Borden	*Registration No. (Attorney/Agent)*	42,344	*Telephone*	(650) 327-3400
Signature				*Date*	04/25/2003

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Signature: Cindy Hoang Date: 4/25/03

APPELLANTS' BRIEF		
Address to: Box AF Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	UCAL121 2429
	First Named Inventor	Y. Huang
	Application Number	09/544,910
	Filing Date	April 7, 2000
	Group Art Unit	1642
	Examiner Name	S.L. Rawlings
	Title	*Methods and compositions for use in the treatment of hyperlipidemia*

#23 (C) 5-1-03

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Final Rejection dated January 13, 2003. No claims have been allowed, and claims 1, 4-8, and 11-35 are pending. All claims are appealed. A Notice of Appeal was filed on February 27, 2003.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815 in the amount of $160.00 to cover the fee required per 37 C.F.R. §1.17(c) for filing Appellants' Brief. No extensions of time are believed necessary, as a Notice of Appeal was filed on February 27, 2003, and this brief is filed within the two-month period from February 27, 2003, i.e., this brief is being filed before April 27, 2003. However, should the Commissioner be of the opinion that additional fees should be paid, Appellants petition for same and authorize the Commissioner to charge such fees to Deposit Account No. 50-0815. In the unlikely event that the check and/or transmittal papers are separated from this document and/or other fees or relief are required, appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number UCAL121.

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REAL PARTY IN INTEREST

The inventors named on this patent application are Yadong Huang, Robert W. Mahley, and John M. Taylor. The inventors assigned their entire rights to the invention to The Regents of the University of California.

RELATED APPEALS AND INTERFERENCES

The undersigned is not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the instant appeal.

STATUS OF THE CLAIMS

This application was filed as a regular U.S. patent application on April 7, 2000, claiming benefit of priority of U.S. Provisional Patent Application No. 60/128,853, filed April 12, 1999.

Claims 1-35 were originally filed. In the response filed on November 9, 2000 to the October 10, 2000 Restriction Requirement, claims 1-11 were elected for prosecution on the merits. Claims 12-35 were withdrawn from consideration. In the response filed on April 30, 2001 to the January 29, 2001 Office Action, claims 1 and 5 were amended. The amendments to claims 1 and 5 were entered. In the response filed on November 8, 2001 to the August 9, 2001 Office Action, claims 2, 3, 9, and 10 were canceled, and claims 1 and 5 were amended. The amendments to claims 1 and 5 were entered. As a result, claims 1, 4-8, and 11 were pending. In the response filed on September 16, 2002 to the May 15, 2002 Office Action, claims 1 and 5 were amended. The amendments to claims 1 and 5 were entered.

The current status of the claims is as follows. Claims 1, 4-8, and 11-35 remain pending. All amendments to claims 1 and 5 have been entered. Pending claims 12-35 remain withdrawn from consideration.

Pending claims 1, 4-8, and 11 shown in attached Appendix I remain pending, rejected, and appealed here.

STATUS OF AMENDMENTS

During the course of prosecution, amendments to claims 1 and 5 were made in amendments filed on April 30, 2001, November 8, 2001, and September 16, 2002, and these amendments were entered.

SUMMARY OF THE INVENTION

The independent claims currently pending are claims 1 and 5. Appellants claim a method for reducing the plasma level of very low density lipoprotein (VLDL) in a host, the method comprising administering to the host an effective amount of an agent which reduces the amount of plasma active apoE in the host by reducing the expression of apoE by an amount sufficient to reduce VLDL production in the host. Appellants further claim a method for treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, the method comprising administering to the host an effective amount of an agent that reduces the plasma amount of active apoE in the host in an amount sufficient to reduce VLDL production by at least two fold.

Hyperlipidemias are conditions of abnormal plasma lipid/lipoprotein/cholesterol levels, and include hypercholesterolemia and hypertriglyceridemia (HTG). HTG is characterized by a proatherogenic lipoprotein profile, including increased plasma triglycerides and very low density lipoprotein (VLDL). HTG is a known risk factor for atherosclerosis and coronary artery disease. A method for reducing plasma VLDL levels would be an effective treatment for hyperlipidemias.

Appellants made the seminal discovery that elevated levels of apoE3 correlate with elevated plasma VLDL in three different mammalian systems, namely mouse, human, and rabbits. Appellants further showed that elevated apoE3 levels lead to elevated plasma VLDL levels. The results of these studies are summarized in the following paragraphs.

1) **Mouse** studies were conducted using transgenic animals that lacked endogenous apoE and that expressed human apoE3 at low levels or at high levels. Specification, page 27, lines 15-26. The mice that expressed high levels of apoE3 had increased VLDL triglyceride and VLDL cholesterol levels, while mice that expressed low levels of apoE3 did not alter triglyceride or VLDL levels significantly. Specification, page 30, lines 18-26; and Table I, Figure 5. Thus, overexpression of apoE3 in transgenic mice alters the plasma lipoprotein profile to one that resembles the human HTG phenotype.

2) **Human** studies were conducted using serum from 27 patients with HTG and 6 normal controls. Specification, page 33, lines 3-15. The HTG subjects had increased plasma triglycerides, increased VLDL cholesterol and triglycerides, and decreased HDL cholesterol; and plasma apoE levels were 2.5- to 4-fold higher than in the normal controls. Specification, page 33, lines 3-15. It was found that the increase in apoE impairs lipoprotein lipase-mediated lipolysis. Specification, page 33, lines 16-22. It was further found that elevated plasma apoE levels cause increased triglyceride levels. Specification, page 33, line 23 to page 34, line 5.

3) **Rabbit** studies were conducted using transgenic rabbits expressing low, medium, or high levels of human apoE3. Specification, page 34, lines 17-27; and page 37, lines 3-8. A direct correlation between high plasma apoE3 levels and elevated cholesterol and triglyceride levels. Specification, page 37, lines 17-23; and Table IV, Figure 15. Elevated plasma apoE3 levels were also positively correlated with elevated plasma VLDL. Specification, page 38, lines 3-18; and Figures 10A-B.

Appellants further recognized that a reduction in plasma VLDL levels could be achieved by reducing plasma apoE levels. Claims under appeal are directed to a method for reducing the plasma level of VLDL in a host, and a method of treating a host suffering from a disease associated with elevated levels of VLDL, the methods comprising administering to the host an effective amount of an agent that reduces the plasma amount of active apoE by reducing expression of apoE by an amount sufficient to reduce VLDL production by at least two fold. Specification, page 9, lines 8-11. Agents for reducing the amount of plasma active

apoE by reducing expression of apoE include small molecules, antisense molecules, and ribozymes. Specification, page 10, lines 1-17; page 14, line 12 to page 15, line 14; and page 16, lines 8-16.

Thus, Appellants identified a correlation between plasma apoE levels and elevated plasma VLDL levels, and provided a method of reducing plasma VLDL levels. Appellants described at least three examples of types of agents that are suitable for use in reducing apoE levels, and hence for reducing VLDL levels.

ISSUES

There are four issues on appeal, as follows:

I. ..... WHETHER THE INVENTION IS DESCRIBED AND DISCLOSED UNDER 35 U.S.C. §112, FIRST PARAGRAPH

II. .....WHETHER THE INVENTION IS ENABLED UNDER 35 U.S.C. §112, FIRST PARAGRAPH

III. .....WHETHER THE CLAIMS COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

IV. .....WHETHER THE INVENTION IS ANTICIPATED UNDER 35 U.S.C. §102(b) BY ANY OF DITSCHUNEIT; YOSHINO; CONNOR; AND KASISKIE

GROUPING OF THE CLAIMS

Claims 1, 4-8, and 11 are directed to treatment methods and are argued as a group. With respect to each ground of rejection set forth in the Final Office Action, claims 1, 4-8, and 11 are argued as a group and stand or fall together.

ARGUMENTS

The arguments portion of this Brief is divided into two sections. The first section describes Appellants' understanding of the Examiner's rejections. The second section specifically addresses the four issues outlined above relating to the written description within the specification of the claimed invention under 35 U.S.C.§112; the support within the specification for the claimed invention under 35 U.S.C. §112; the compliance of the claims with the requirements of 35 U.S.C.§112, second paragraph; and the novelty of the invention over the cited art under 35 U.S.C.§102(b).

THE EXAMINER'S REJECTIONS

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. It was the Examiner's position that the specification fails to set forth exemplification that might demonstrate that the invention can be used successfully to reduce the plasma level of VLDL and triglycerides in a host. It was the Examiner's position that the specification fails to set forth exemplification that might demonstrate that the invention can be used efficaciously to treat a host suffering from a disease condition associated with elevated levels of VLDL and/or triglycerides.

The specification was objected to under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Based on the objection to the specification, claims 1, 4-8, and 11 were rejected under 35 U.S.C. §112, first paragraph. It was the Examiner's position that the specification fails to provide any guidance, direction, or working examples of a method for reducing plasma VLDL levels, or for treating a host suffering from a disease condition associated with elevated plasma levels of VLDL.

Claims 5 and 11 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite. It was the Examiner's position that claims 5 and 11 are vague and indefinite for reciting the phrase "a disease condition associated with elevated plasma levels of VLDL." It was the Examiner's position that it cannot be

ascertained how the disease condition is required by the claim to be associated with elevated plasma levels of VLDL.

Claims 1, 4-8, and 11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ditschuneit et al. ((1992) *J. Int'l. Med. Res.* 20:197-210; "Ditschuneit") as evidenced by Pedreño et al. ((2000) *Metabolism* 49:942-949; "Pedreño") and Durrington et al. ((1998) *Atherosclerosis* 138:217-225; "Durrington"). The Examiner stated that Ditschuneit teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides; and that Ditschuneit administers to the patients an effective amount of gemfibrozil to reduce the concentrations of VLDL and triglycerides. The Examiner asserted that Pedreño teaches that gemfibrozil causes a reduction in the level of plasma active apoE. It was the Examiner's position that, in view of the teachings of Pedreño and of Durrington, the method of Ditschuneit causes a reduction in plasma active apoE.

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Yoshino et al. ((1989) *Atherosclerosis* 75:67-72; "Yoshino"). The Examiner stated that Yoshino teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides; and that Yoshino administers to the patients an effective amount of pravastatin to reduce the concentrations of apoE, VLDL, and triglycerides in the patient's plasma. It was the Examiner's position that Yoshino teaches that the actual levels of apoE in the plasma of patients treated with pravastatin is decreased.

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Connor et al ((1993) *Ann. N.Y. Acad. Sci.* 683:16-34; "Connor"). The Examiner stated that Connor teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides; and that Connor administers to the patients an effective amount of dietary n-3 fatty acids to reduce the concentration of apoE, VLDL, and triglycerides in the patient's plasma. It was the Examiner's position that Connor teaches that the actual level of apoE in the plasma of patients treated with pravastatin is decreased, indicating a reduction in the level of apoE has occurred as a result of the treatment.

Claims 1, 5, 6, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Kasiskie et al. ((1990) *Am. J. Kidney Dis.* 15:8-15; "Kasiskie") as evidenced by Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; "Wyne"). The Examiner stated that Kasiskie teaches a method of treating patients diagnosed with a hyperlipidemia, involving administering to a patient an effective amount of lovastatin to

reduce production of VLDL in the patient. The Examiner further stated that Wyne teaches that lovastatin attenuates production of mRNA encoding apoE in cells. It was the Examiner's position that Kasiskie's method involved reducing apoE expression.

APPLICANTS' RESPONSE TO THE REJECTIONS

1) The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, first paragraph, as allegedly lacking written description is in error. Appellants have provided a detailed list of at least three different classes of agents suitable for use in the present invention. Appellants' discovery that elevated apoE expression is associated with elevated plasma VLDL levels, coupled with the description in the specification and that which is known in the art, would reasonably convey to the skilled artisan that Appellants were in possession of the claimed invention as of the filing date. Accordingly, claims 1, 4-8, and 11 meet the written description requirements of 35 U.S.C.§112, first paragraph.

2) The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is in error. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Practice of the claimed methods would not require undue experimentation because a) the sequence of an apoE gene is known; b) guidance is given on how to test whether a give agent reduces apoE gene expression to a level sufficient to reduce VLDL production; c) there is ample guidance in the art for how to make and use agents, such as antisense nucleic acids, that reduce apoE expression; and d) one of skill in the art would be able to perform, as a matter of routine, experiments to determine whether a given agent reduces apoE expression to the requisite degree. Accordingly, claims 1, 4-8, and 11 meet the enablement requirement of 35 U.S.C.§112, first paragraph.

3) The rejection of claim 5 and 11 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is in error. The Examiner was of the position that the phrase "a disease condition associated with elevated plasma levels of VLDL" is unclear. The specification discusses disorders, including Type IV hyperlipidemia

and Type IIb hyperlipidemia, that are associated with elevated plasma VLDL levels. Furthermore, disorders associated with elevated plasma VLDL levels are known in the art. In view of the disclosure in the specification and the knowledge in the art regarding such disorders, the phrase "a disease condition associated with elevated plasma levels of VLDL" in claims 5 and 11 is clear. Accordingly, claims 5 and 11 meet with the requirements of 35 U.S.C.§112, second paragraph.

4) The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Ditschuneit is in error. Ditschuneit discusses administering gemfibrozil. Gemfibrozil does not reduce expression of apoE. Therefore, Ditschuneit does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Ditschuneit cannot anticipate claims 1, 4-8, and 11.

5) The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Yoshino is in error. Yoshino discusses administering pravastatin. Pravastatin does not reduce expression of apoE. Therefore, Yoshino does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Yoshino cannot anticipate claims 1, 4-8, and 11.

6) The rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Connor is in error. Connor discusses administering dietary n-3 fatty acids. Connor states that dietary n-3 fatty acids caused a reduction in LDL. This is the opposite effect on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE and would lead one of skill in the art to believe that the mechanism of action is not through a reduction in apoE gene expression. Dietary n-3 fatty acids do not reduce expression of apoE. Therefore, Connor does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Connor cannot anticipate claims 1, 4-8, and 11.

7) The rejection of claims 1, 5, 6, and 11 under 35 U.S.C. §102(b) as allegedly anticipated by Kasiskie is in error. Kasiskie discusses administering lovastatin. Lovastatin does not reduce apoE gene expression. Therefore, Kasiskie does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE. Accordingly, Kasiskie cannot anticipate claims 1, 5, 6, and 11.

I. WHETHER THE INVENTION IS DESCRIBED UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Final Office Action stated that claims 1, 4-8, and 11 were rejected for the reasons set forth in Office Actions mailed January 29, 2002, August 9, 2001, and May 15, 2002. The May 15, 2002 Office Action stated that the specification fails to set forth exemplification that might demonstrate that the invention can be used successfully to reduce the plasma level of VLDL and triglycerides in a host. The May 15, 2002 Office Action stated that the specification fails to set forth exemplification that might demonstrate that the invention can be used efficaciously to treat a host suffering from a disease condition associated with elevated levels of VLDL and/or triglycerides.

Claims 1, 4-8, and 11 meet the written description requirement of 35 U.S.C.§112, first paragraph. All that is necessary to fulfill the written description requirement of 35 U.S.C.§112, first paragraph, is that one of skill in the art recognize that applicants invented what is claimed. MPEP §2163.02. Appellants have disclosed the novel discovery that overexpression of apoE causes HTG. As discussed in detail below, Appellants have provided a detailed list of numerous agents suitable for use in the present invention. Appellants' discovery, coupled with the description in the specification and that which is known in the art, would reasonably convey to the skilled artisan that Appellants were in possession of the claimed invention as of the filing date.

The Examiner failed to establish sufficient grounds for the assertion that claims 1, 4-8, and 11 lack adequate written description. The Examiner merely stated that "in the absence of factual evidence, the

skilled artisan would not reasonably conclude that Applicants had possession of the claimed invention at the time the application was filed" and "[e]vidence of contemplation is not evidence of a reduction to practice, or evidence that Applicants had possession of the claimed invention." May 15, 2002 Office Action, page 4.

The May 15, 2002 Office Action asserted that no factual evidence was presented to indicate that Appellants had "successfully practiced at least a substantial number of the methods encompassed by the claims." May 15, 2002 Office Action, page 4. However, fulfillment of the written description requirement of 35 U.S.C.§112, first paragraph, does not require that Applicants provide evidence of having successfully practiced the invention. To satisfy the written description requirement, Applicants need only reasonably convey to a person of ordinary skill in the relevant art that Applicants were in possession of the claimed subject matter. "In possession of" is not synonymous with "successfully practiced." The inquiry into whether the description requirement is a question of fact. The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. The Examiner has provided no such evidence.

The Final Office Action stated: "Applicants' disclosure does not include a description of at least a substantial number of embodiments of the methods encompassed by the claims; nor does Applicants' disclosure include a description of at least a representative number of embodiments of the methods encompassed by the claims." Bridging paragraph, pages 6-7. It is unclear what exactly is meant by this statement.

The Final Office Action further stated: "the claims encompass a large genus of widely variant species and thus an adequate written description of the claimed invention must include sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus." Final Office Action, page 4.

However, with respect to agents to be administered to reduce the amount of plasma active apoE in a host, the specification provides a description of at least three types of agents that can be used in the claimed methods.

1) The specification states that **small molecules** are useful for reducing plasma active apoE. Specification, page 10, lines 1-17. The specification states that the agent may be an apoE inhibitor. Specification, page 10, lines 2-6.

2) The specification states that **antisense molecules** are useful for reducing expression of apoE. Specification, page 14, line 12 to page 15, line 14. The nucleotide sequences of mRNA encoding apoE were known as of the effective filing date of the instant application. For example, the specification provides the GenBank accession numbers providing mRNA sequences of human apoE2, apoE3, and apoE4. Specification, page 15, lines 7-10. Because the nucleotide sequences of apoE mRNAs are known, the sequences of antisense are also known, and need not be provided in the specification. Applicants note that it is well established that a "patent need not teach, and preferably omits, what is well known in the art." MPEP §2164.01. Because the nucleotide sequence of genes encoding apoE, e.g., apoE3 were known, those skilled in the art would reasonably expect that one could use antisense technology to reduce apoE expression. Thus, those skilled in the art would have recognized that Appellants were in possession of the claimed invention, where the agent is an antisense molecule.

3) The specification states that **ribozymes** are useful for reducing expression of apoE. Specification, page 16, lines 8-16. As discussed above, the nucleotide sequence of mRNA encoding apoE were known as of the effective filing date of the instant application. Because the nucleotide sequence of genes encoding apoE, e.g., apoE3 were known, those skilled in the art would reasonably expect that one could use ribozyme technology to reduce apoE expression. Therefore, those skilled in the art would have recognized that Appellants were in possession of the claimed invention, where the agent is a ribozyme.

The Final Office Action stated that antisense technology is "highly unpredictable." Final Office Action, page 5. The Office Action cited Sohail and Southern ((2000) *Curr. Opinions Mol. Ther.* 2:264:271;

"Sohail"); Pierce et al. ((1998) *Nucl. Acids Res.* 26:5093-5101; "Pierce"); and Lesoon-Wood et al. ((1999) *Cancer Letters* 147:163-173; "Lesoon-Wood") as evidence of the alleged unpredictability of antisense technology.

Sohail states that predicting the optimal sequence of an antisense nucleic acid that will bind to a given sense nucleic acid is difficult. However, Sohail states that empirical approaches to identifying an antisense nucleic acid that hybridizes with a given sense nucleic acid are successful. Thus, one cannot conclude from reading Sohail that antisense technology as a whole is unpredictable, since empirical determination of antisense sequences results in success. At most one can conclude that some experimentation is involved to identify an antisense nucleic acid that will hybridize with a given sense nucleic acid. As discussed above, a substantial amount of experimentation is allowed, if it is routine; and such experimentation would in fact be routine.

Pierce merely discusses predicting the optimal sequence of a ribozyme nucleic acid. Pierce discusses a method for identifying ribozymes that are effective in modulating gene expression. Thus, one cannot conclude from Pierce that antisense is unpredictable, since Pierce discusses methods for identifying functional ribozymes.

Lesoon-Wood report that control antisense molecules caused a considerable level of non-specific inhibition. However, such activity on the part of control antisense nucleic acids is the exception, rather than the rule. An isolated reference discussing problems that researchers may have had with particular antisense does not lead to a conclusion that the instant invention as claimed is not enabled. Furthermore, the instant claims require that the agent reduce apoE levels to a degree sufficient to reduce VLDL production. Agents that do not have such activity are not within the scope of the claim. However, isolated reports of problems associated with a particular application of antisense technology does not render the entire art unpredictable. Failures occur even in "predictable" arts.

The Examiner has ignored the fact that the overwhelming body of literature points to many successes with antisense technology. For example, Charpentier et al. ((2000) *Biochemistry* 39:16084-91, a copy of

which was provided along with the response to the Office Action mailed August 9, 2001) **have already demonstrated that antisense technology can be used to reduce apoE expression**. Charpentier discloses the use of apoE antisense to reduce apoE gene expression in eukaryotic cells. Charpentier, Abstract; page 16085, and column 2, first full paragraph.

Appellants have provided a detailed list of numerous agents suitable for use in the present invention. Appellants' discovery, coupled with the description in the specification and that which is known in the art, would reasonably convey to the skilled artisan that Appellants were in possession of the claimed invention as of the filing date. Accordingly, claims 1, 4-8, and 11 meet the written description requirements of 35 U.S.C.§112, first paragraph.

II. WHETHER THE INVENTION IS ENABLED UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Final Office Action stated the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims and would be insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention to reduce the plasma level of VLDL in a host, or to treat a host suffering from a disease associated with elevated levels of VLDL without need of performing additional, undue experimentation.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The specification provides ample guidance such that one skilled in the art could use the specification, coupled with that which is known in the art, to practice the claimed invention. Applicants describe several methods of decreasing expression of apoE on page 14, line 12 through page 16, line 16. Once a skilled artisan has identified a gene target, reducing its expression is well within that artisan's skill. For example, since the nucleotide sequence of apoE is known, one of skill in the art would fully expect to be able to use antisense technology to reduce apoE expression. Furthermore, researchers, such as Charpentier et al. ((2000) *Biochemistry* 39:16084-91, a copy of which was provided along with the response to the Office Action mailed August 9, 2001) **have already demonstrated that antisense technology can be used to reduce apoE expression**.

Appellants respectfully submit that the specification and the claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

(a) the quantity of experimentation necessary:

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to

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2 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

3 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[5]

The claims recite methods involving reducing the amount of plasma active apoE in a host by reducing the expression of apoE in the host. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which factors, such as antisense, small molecules that affect expression, ribozymes, and the like, that reduce expression of apoE. As an example, the sequence of an antisense nucleic acid that reduces apoE expression is determined through routine experimentation that is standard in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of antisense nucleic acids made by routine recombinant DNA techniques. For example, a suitable assay for determining the effect of apoE expression levels on VLDL triglyceride production *in vitro* is described in the specification on page 29, line 21 to page 30, line 7. In this assay, rat hepatoma cells transfected *in vitro* with an apoE-encoding construct were assayed for VLDL production, and the effect of the level of apoE expression on VLDL production was studied. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the level of VLDL production, and since this only requires a routine assay on various antisense nucleic acids to determine the effects of same on VLDL production, no undue experimentation is necessary.

(b) the presence or absence of working examples:

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad

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4 *In re Wands* 8 USPQ 2d at 1404
5 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

terminology or illustrative examples."[7]

(c) the relative skill of those in the art:

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

Furthermore, as discussed above, several texts exist (in addition to abundant literature in scientific journals), which provide ample description of how to make and use antisense nucleic acids. Still further, those skilled in the art are well aware of how to modulate expression of a gene, once the sequence of the gene is known.

A search of the PubMed database (available via the National Center for Biotechnology Information web server) for the word "antisense" in the title of an article resulted in 4178 articles about uses of antisense technology (the first 25 pages of the search results were provided as Exhibit A along with the amendment, filed on November 8, 2001 and responsive to the August 9, 2001 Office Action). For example, Sze et al. (Neurochem. Int. (2001) 39:319-327 (a copy of which was provided along with the amendment, filed on November 8, 2001 and responsive to the August 9, 2001 Office Action)) reports the successful use of antisense to block both the mRNA and protein expression of NR2B in neurons and Finegold et al. ((2001) *Mol. Brain Res.* 90:17-25 (a copy of which was provided along with the amendment, filed on November 8, 2001 and responsive to the August 9, 2001 Office Action)) reports the development of an antisense gene therapy to modulate the NMDA type of glutamate receptor. Furthermore, as noted above, Charpentier demonstrates the use of antisense technology to reduce expression of apoE.

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6 In re Borkowski, 164 USPQ at 645.
7 *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

Antisense technology has also reached the point where numerous antisense oligonucleotides are in clinical trials. For example, Tamm et al. ((2001) *Lancet* 358:489-497 (a copy of which was provided along with the amendment, filed on November 8, 2001 and responsive to the August 9, 2001 Office Action)) provides an overview of antisense therapy and provides a list of antisense oligonucleotides that are either in clinical trials or are already approved for use (see page 490). Agrawal and Kandimalla ((2000) *Mol. Med. Today* 6:72-81 (copy provided along with response to August 9, 2001 Office Action)) list 16 antisense oligonucleotides that are being investigated for clinical use in treating oncological, hematological and viral diseases (see page 74). The article concludes with the following statement:

> Many questions about the effects of **antisense oligonucleotide** sequence, secondary structures, cellular uptake, metabolism, excretion, tissue distribution, side effects and mechanism of action have been answered to a large extent, if not completely, in the past few years.

Page 80 (emphasis in original). Thus, contrary to the assertions contained in the Office Action, the use of antisense technology to reduce gene expression is well within the ability of one skilled in the art and would require no more than routine experimentation.

(d) the predictability or unpredictability of the art

In making this rejection, the May 15, 2002 Office Action asserted that the antisense art is unpredictable, and two references are provided in support of this argument. The May 15, 2002 Office Action asserted that because the art is unpredictable, the specification is not enabling.

The May 15, 2002 Office Action cited various references to support the contention that antisense technology is unpredictable. However, the May 15, 2002 Office Action merely presented isolated references discussing problems associated with the technology. There are problems associated with every technology. Antisense technology is no exception. The possibility that there may be problems does not lead to a conclusion that the instant specification lacks enablement. Furthermore, the overwhelming consensus in the field -- as evidenced by the above-cited texts, other texts not cited herein, as well as the thousands of literature references describing successful application of antisense technology, the fact that numerous clinical

trials are underway which employ antisense technology -- is that antisense technology works, and that those in the field, given the sequence of a gene, can make and use antisense nucleic acids.

The May 15, 2002 Office Action cited Sohail et al. ((2000) *Curr. Opinions Mol. Ther.* 2:264:271; "Sohail"); and Pierce et al. ((1998) *Nucl. Acids Res.* 26:5093-5101; "Pierce") to support the assertion that antisense technology is unpredictable. Sohail states that predicting the optimal sequence of an antisense nucleic acid that will bind to a given sense nucleic acid is difficult. However, Sohail states that empirical approaches to identifying an antisense nucleic acid that hybridizes with a given sense nucleic acid are successful. Thus, one cannot conclude from reading Sohail that antisense technology as a whole is unpredictable, since empirical determination of antisense sequences results in success. At most one can conclude that some experimentation is involved to identify an antisense nucleic acid that will hybridize with a given sense nucleic acid. As discussed above, a substantial amount of experimentation is allowed, if it is routine; and such experimentation would in fact be routine. As with Sohail, Pierce merely discusses predicting the optimal sequence of a ribozyme nucleic acid. Pierce discusses a method for identifying ribozymes that are effective in modulating gene expression. Thus, one cannot conclude from Pierce that antisense is unpredictable, since Pierce discusses methods for identifying functional ribozymes.

Indeed, the findings of Charpentier et al., which demonstrated that antisense technology can be used to reduce apoE expression, appear to contradict the assertion that antisense technology is unpredictable.

The May 15, 2002 Office Action stated that delivery of antisense agents has wrought undesirable, adverse, non-specific toxicity. However, issues of toxicity and unwanted side effects are outside of the purview of the U.S. Patent and Trademark Office. Instead, such issues are addressed by the FDA. See MPEP §2107.02, section V. As stated in the MPEP (§2107.02, section V), it is improper for Office personnel to request evidence of safety in the treatment of humans.

The May 15, 2002 Office Action stated that Lesoon-Wood et al. ((1999) *Cancer Letters* 147:163-173; "Lesoon-Wood") discovered that control antisense molecules caused a considerable level of non-specific inhibition. However, such activity on the part of control antisense nucleic acids is the exception, rather than the rule. An isolated reference discussing problems that researchers may have had with particular antisense does not lead to a conclusion that the instant invention as claimed is not enabled. Furthermore, the instant claims require that the agent reduce apoE levels to a degree sufficient to reduce VLDL production. Agents that do not have such activity are not within the scope of the claim.

The May 15, 2002 Office Action asserted that there is evidence that reducing the level of apoE expression in a host may not be an effective means for treating a patient diagnosed with a disease associated with dyslipidemia. In support of this statement, the May 15, 2002 Office Action cited Ishigami et al. ((1998) *J. Biol. Chem.* 273:20156-20161; "Ishigami"); and Huang et al ((1998) *J. Biol. Chem.* 273:26388-26393; "Huang"). Ishigami discusses protective effects of apoE through inhibition of cell signaling events associated with growth factor-induced smooth muscle cell migration and proliferation; and Huang discusses problems associated with too low levels of apoE. However, a reduction in apoE expression to an extent sufficient to reduce VLDL does not preclude a protective effect of apoE against vascular disease. As an analogous situation, an increase over a certain threshold in the plasma level of glucose is quite harmful, while a lower level of plasma glucose is beneficial and indeed necessary for normal human functioning. The fact that a high level of plasma glucose is harmful, while lower levels of plasma are beneficial does not present a paradox. One can reduce pathologically high levels of glucose to treat diabetes without vitiating the beneficial effects of normal plasma glucose levels. In an analogous manner, a reduction in apoE gene expression can lead to a reduction in plasma VLDL levels without vitiating any protective or beneficial effects of apoE.

The Examiner has not produced any reasoning why a reduction in apoE expression to an extent sufficient to reduce VLDL would preclude a protective effect of apoE against vascular disease. The Examiner has not substantiated the assertion that "reducing the level of apoE expression in a host may not be an effective means for treating a patient diagnosed with a disease associated with dyslipidemia."

The May 15, 2002 Office Action stated that the courts have determined that antisense technology is highly unpredictable, citing *Enzo Biochem. Inc., v. Calgene, Inc.* 52 USPQ2d 1129 (Fed. Cir., 1999); "*Enzo*." However, *Enzo* does not support a conclusion that the instant claims are not enabled. As noted in *Enzo*, whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed. The patents in question in *Enzo* had an effective filing date of October 20, 1983. As stated in *Enzo*, "an enablement determination is made retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time. *Enzo* at 1134. A finding of lack of enablement of a patent having an effective filing date of October 20, 1983 cannot justifiably be applied to the instant patent application having an effective filing date of March 12, 1999, because the field has advanced profoundly in the intervening 16 years.

Furthermore, *Enzo* is a review of patent claims that "attempt to include the entire universe of cells for the antisense system detailed." *Enzo*, at 1134. The instant claims are not directed to "a prokaryotic or eukaryotic cell containing a non-native DNA construct, which construct produces an RNA which regulates the function of a gene," as did the patents under review in *Enzo*. Instead, the instant claims recite use of an agent that reduces expression of a apoE, for which the sequence was known as of the effective filing date.

Furthermore, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments

8 *In re Angstadt*, 190 USPQ at 218.

which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

(e) the breadth of the claims

The claims of the instant application only require that the level of apoE expression be reduced by an amount sufficient to reduce VLDL production. *Thus, the claim language excludes agents that do not reduce apoE expression to such an amount.*

Those skilled in the art are well aware of variety of agents that reduce expression of a coding region, including agents that affect promoter activity, antisense nucleic acids, and ribozymes.

In sum, the amount of experimentation required to practice the claimed methods would not be undue because a) the sequence of an apoE gene is known; b) guidance is given on how to test whether a give agent reduces apoE to a level sufficient to reduce VLDL production; c) there is ample guidance in the art for how to make and use agents, such as antisense nucleic acids, that reduce apoE expression; and d) one of skill in the art would be able to perform, as a matter of routine, experiments to determine whether a given agent reduces apoE expression to the requisite degree.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. As such, claims 1, 4-8, and 11 meet the enablement requirement of 35 U.S.C.§112, first paragraph.

III. WHETHER THE CLAIMS COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

The Final Office Action stated that claims 5 and 11 are vague and indefinite for reciting the phrase "a disease condition associated with elevated plasma levels of VLDL." The Final Office Action stated that it cannot be ascertained how the disease condition is required by the claim to be associated with elevated plasma levels of VLDL.

The specification provides a discussion of disorders associated with elevated plasma levels of VLDL. Specification, page 19, lines 12-25. The specification states that disorders associated with elevated plasma levels of VLDL include Type IV hyperlipidemia and Type IIb hyperlipidemia. Specification, page 19, lines 21-25. The specification further discusses various plasma levels of VLDL that are considered to be elevated. Specification, page 19, lines 15-17. Furthermore, disorders associated with elevated plasma levels of VLDL are known in the art.

In view of the discussion in the specification regarding disorders associated with elevated VLDL levels, and the knowledge in the art regarding such disorders, the phrase "a disease condition associated with elevated plasma levels of VLDL" in claims 5 and 11 is clear. Accordingly, claims 5 and 11 meet with the requirements of 35 U.S.C.§112, second paragraph.

IV. WHETHER THE INVENTION IS ANTICIPATED UNDER 35 U.S.C. §102(b) BY DITSCHUNEIT; BY YOSHINO; BY CONNOR; OR BY KASISKIE

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Ditschuneit et al. ((1992) *J. Int'l. Med. Res.* 20:197-210; "Ditschuneit") as evidenced by Pedreño et al. ((2000) *Metabolism* 49:942-949; "Pedreño") and Durrington et al. ((1998) *Atherosclerosis* 138:217-225; "Durrington"). Claims 1, 3-8, 10, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Yoshino et al. ((1989) *Atherosclerosis* 75:67-72; "Yoshino"). Claims 1, 3-8, 10, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Connor et al ((1993) *Ann. N.Y. Acad. Sci.* 683:16-34; "Connor"). Claims 1, 5, 6, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Kasiskie et al. ((1990) *Am. J. Kidney Dis.* 15:8-15; "Kasiskie") as evidenced by Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; "Wyne").

Before the above rejections over the cited art are addressed, Appellants provide comments regarding the inherency anticipation, and provide comments regarding the claims.

Comments regarding inherency anticipation

According to the law, a reference may anticipate a claim even if a feature recited in the claim is not specifically disclosed in the reference. However, the law has established that where the reference is silent as to a specific limitation in the claims, such a gap in the reference must be filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill in the art* at the time the invention was made. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749-1750 (Fed. Cir. 1991). The characteristic must flow *undeniably and irrefutably* from the express disclosures of the prior art reference. Mere possibilities or even probabilities are not enough to support a finding of anticipation. *Motorola, Inc. v. Interdigital Technology Corp.*, 43 USPQ 2d 1481 (Fed. Cir. 1997). In relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd.Pat.App.& Inf. 1990).

Comments regarding the claims

Claims 1 and 5 were amended in the amendment, filed November 8, 2001 and responsive to the August 9, 2001 Office Action, to recite administering an agent that reduces the amount of plasma active apoE "by reducing the expression of apoE."

The May 15, 2002 Office Action asserted that the claims are not limited to a method in which the level of transcription of the gene encoding apoE is reduced, or in which the level of translation of mRNA encoding apoE is reduced. However, the claims recite administering an agent that acts by "**reducing the expression of apoE**." "Reducing the expression of apoE" is an art term understood by those in the field to refer to reducing transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE.

None of the cited art discloses or suggests a method of reducing the plasma level of VLDL in a host, the method comprising administering to the host an effective amount of an agent that reduces the amount of

plasma active apoE in said host **by reducing the expression of apoE** by an amount sufficient to reduce VLDL production in the host to reduce the plasma level of VLDL in the host, whereby the plasma level of VLDL in the host is reduced by at least two fold. It does not flow *undeniably and irrefutably* from the express disclosures of the cited references that the agents discussed therein reduce apoE gene expression.

Each of the rejections over the cited art is addressed in turn in the following paragraphs.

a) Claims 1, 4-8, and 11 over Ditschuneit as evidenced by Pedreño and by Durrington

The Final Office Action stated that claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as anticipated by Ditschuneit as evidenced by Pedreño and by Durrington for the reasons set forth in the Office Actions mailed January 29, 2001, August 9, 2001, and May 15, 2002.

The January 29, 2001 Office Action stated that Ditschuneit et al. teaches a method of treating female patients with hyperlipoproteinaemia type IV with gemfibrozil and that the mechanism by which an agent acts to treat a disease is an inherent property of that agent. The January 29, 2001 Office Action then pointed to Pedreño and Durrington, asserting that they teach that gemfibrozil causes a reduction in levels of triglyceride, VLDL and apoE in a patient. The January 29, 2001 Office Action asserted that all the limitations of the claims are anticipated by the teachings of Ditschuneit.

Ditschuneit discusses administration of gemfibrozil to patients. Gemfibrozil increases LDL receptor expression. The instant claims recite use of an agent that reduces expression of apoE. **Gemfibrozil does not reduce expression of apoE**. Nothing in the cited references teaches that gemfibrozil reduces expression of apoE. Thus, the claimed invention and the methods using gemfibrozil are not the same. Accordingly, Ditschuneit, as evidenced by Pedreño and Durrington, does not anticipate claims 1, 4-8, and 11.

Nothing in either Pedreño or Durrington provides the showing required by law to support the rejection based on the alleged inherent property of gemfibrozil. In fact, the common knowledge in the art, as evidenced by the abstract mentioned above, is that the mechanism of action of gemfibrozil is through

increasing LDL receptor expression, for which apoE is a ligand. Since apoE is a component of VLDL, an increase in LDL receptor will result in enhance clearance of plasma VLDL (*see* Huang, page 26388, right column). Further, because apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL clearance is increased. However, **this decrease in apoE is not a decrease in expression of apoE**, as the claims require.

The May 15, 2002 Office Action asserted that the claims are not limited to a method in which the level of transcription of the gene encoding apoE is reduced, or in which the level of translation of mRNA encoding apoE is reduced. However, the claims recite administering an agent that acts by "**reducing the expression of apoE**." "Reducing the expression of apoE" is an art term understood by those in the field to refer to reducing transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE.

The May 15, 2002 Office Action stated that "it is reasonable to expect that gemfibrozil affects the expression of apoE." May 15, 2002 Office Action, page 12. However, this is an assertion without basis in fact. The Examiner has presented no evidence whatsoever that gemfibrozil affects the expression of apoE.

The Examiner stated that gemfibrozil is deemed the same as the agent of the present claims. The initial burden is on the Examiner to provide reasoning or facts to substantiate the assertion that gemfibrozil affects expression of apoE. MPEP §2112. The Examiner has not provided such reasoning or facts.

The Final Office Action stated that Appellants have not provided any factual evidence to support the assertion that gemfibrozil does not reduce the expression of apoE. In fact, since the Examiner initially asserted that gemfibrozil reduces expression of apoE, the burden of proof is on the Examiner to provide evidence of such an effect. Absent such evidence, a rejection of the instant claims as anticipated by Ditschuneit is improper. As discussed above, in relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd.Pat.App.& Inf. 1990). Furthermore, as Appellants have repeatedly explained,

gemfibrozil is known in the art to increase LDL receptor expression, for which apoE is a ligand. Since apoE is a component of VLDL, an increase in LDL receptor will result in enhance clearance of plasma VLDL. Further, because apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL clearance is increased; however, **this decrease in apoE is not a decrease in expression of apoE**, as the claims require.

The May 15, 2000 Office Action stated that Clavey et al. ((1999) *Cell. Physiol. Biochem.* 9:139-149; "Clavey") reported that fibrates repress apolipoprotein CIII gene expression. The Office Action concluded that the mechanism of gemfibrozil is not limited to increasing LDL receptor expression. However, Clavey does not disclose any effect of gemfibrozil on apoE expression. The Office Action has provided no basis for extrapolating an effect on apolipoprotein CIII gene expression to an effect on expression of any other gene.

In view of the fact that Ditschuneit does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE, Ditschuneit cannot not anticipate claims 1, 4-8, and 11, and this rejection under 35 U.S.C. §102(b) should be reversed.

b) Claims 1, 4-8, and 11 over Yoshino

The Final Office Action stated that claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as anticipated by Yoshino for the reasons set forth in the Office Actions mailed January 29, 2001, August 9, 2001, and May 15, 2002.

The January 29, 2001 Office Action stated that Yoshino teaches that treating patients with pravastatin results in a significant decrease in the levels of triglyceride, VLDL, and apoE in the plasma of the patients.

Yoshino discusses administration of pravastatin to patients with hyperlipidemic non-insulin dependent diabetes. Yoshino neither discloses nor suggests that apoE is a target for reducing VLDL

production. Yoshino neither discloses nor suggests a method for reducing plasma levels of VLDL, comprising administering an agent that reduces apoE expression, as required by the claims.

As discussed above for gemfibrozil, there is no evidence that pravastatin acts to decrease VLDL production by reducing expression of apoE, while there is evidence that it acts through a different mechanism in that it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This inhibition of HMG-CoA reductase leads to upregulation of the LDL receptor, which, in turn, leads to enhanced clearance of plasma VLDL. Since apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL is cleared; however, this decrease in apoE is not a direct effect of the agent as the claims require. In addition, if pravastatin decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE, but it does not. Huang states:

> ...apoE is a ligand for the LDL receptor, cell-surface heparan sulfate proteoglycans, and the LDL receptor-related protein. Thus, apoE accumulation in the VLDL would effectively mediate the clearance of the VLDL from plasma and, at the same time, impair lipolytic processing of the VLDL to LDL. The combined effect of apoE in VLDL clearance and lipolysis would result in decreased LDL. In fact, plasma LDL cholesterol levels in [hypertriglyceridemia] patients are normal or slightly decreased.

Huang, page 26393. Thus, increased apoE results in normal or decreased LDL levels; however, Yoshino shows a significant decrease in LDL cholesterol levels after 6 months of treatment with pravastatin and a further decrease by the 12th month of treatment (page 68, right column, last full paragraph). This is the opposite effect on LDL cholesterol that would be expected if pravastatin decreased VLDL production by decreasing apoE expression, and would lead one of skill in the art to believe that the mechanism of action is not through apoE.

The Final Office Action acknowledged that pravastatin is known to act as an inhibitor of HMG-CoA reductase. However, the Final Office Action stated "since Wyne, et al teach that another inhibitor of HMG-CoA reductase, namely mevinolin acts to attenuate the expression of *apoE* it is clear that although an agent is known to be an inhibitor of HMG-CoA, one cannot rule out the **possibility** that the agent also acts to inhibit the expression of ApoE." Final Office Action, page 11, emphasis added; citing Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; "Wyne").

First, Wyne does not discuss pravastatin. Furthermore, Wyne states that HMG-CoA reductase is a rate-limiting enzyme in cholesterol synthesis and as such reduces the level of downstream products. Wyne does not disclose that mevinolin, or any other inhibitor of HMG-CoA reductase, reduces apoE expression.

Second, as noted above, mere **possibilities** or even probabilities are not enough to support a finding of anticipation. *Motorola, Inc. v. Interdigital Technology Corp.,* 43 USPQ 2d 1481 (Fed. Cir. 1997). In relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd.Pat.App.& Inf. 1990). Should the Examiner have any evidence that pravastatin reduces expression of apoE, the Examiner is requested to provide such evidence in an affidavit, as provided for under 37 C.F.R.§1.104(d)(2).

Third, Appellants have already met their burden of proof, by presenting evidence that pravastatin does not reduce expression of apoE, as required by the claims.

In view of the fact that Yoshino does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE, Yoshino cannot not anticipate claims 1, 4-8, and 11, and this rejection under 35 U.S.C. §102(b) should be reversed.

c) Claims 1, 4-8, and 11 over Connor

The Final Office Action stated that claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as anticipated by Connor for the reasons set forth in the Office Actions mailed January 29, 2001, August 9, 2001, and May 15, 2002.

The January 29, 2001 Office Action stated that Connor teaches a method of treating hypertriglyceridemic patients, comprising administering dietary n-3 fatty acids; and that Connor teaches a dramatic reduction in plasma triglycerides resulting from the treatment, as well as a decrease in the levels of VLDL and apoE. The January 29, 2001 Office Action concluded that Connor teaches that the actual level of apoE in the plasma decreased, indicating that a reduction in the level of expression of apoE has occurred as a result of the treatment.

Nothing in Connor teaches that apoE is a target for reducing levels of VLDL production or that reduction of apoE gene expression will cause a reduction in VLDL production. Furthermore, there is nothing that suggests that n-3 fatty acids act to decrease VLDL production by reducing apoE expression, while there is evidence that n-3 fatty acids act through a different mechanism. As noted above, if the cited agent decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE. Huang teaches that increased apoE results in normal or decreased LDL levels; however, Connor states that dietary n-3 fatty acids caused a reduction in LDL. This is the **opposite effect** on LDL level that would be expected if n-3 fatty acids acted by decreasing active apoE by decreasing gene expression, and would lead one of skill in the art to believe that the mechanism of action is not through apoE.

Connor further states that dietary n-3 fatty acids reduce synthesis of triglyceride and VLDL in the liver and shorten turnover of VLDL in the plasma. This statement is supported by both Harris ((1989) *J. Lipid Res.* 30:785-807 (abstract provided along with the response to the August 9, 2001 Office Action)) and Hebbachi et al. ((1997) *Biochem. J.* 325:711-9 (abstract provided along with the response to the August 9, 2001 Office Action)). Furthermore, Anil et al. ((1997) *Biochem. Mol. Biol. Int.* 43:1071-80 (abstract

provided along with the response to the August 9, 2001 Office Action)) report that the effect of n-3 fatty acids on hepatic VLDL production is mediated through prostaglandins. Nothing in the references teach that dietary n-3 fatty acids reduce expression of apoE or that reducing apoE expression will reduce VLDL production and consequently reduce the plasma VLDL level.

In view of the fact that Connor does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by reducing the expression of apoE, Connor cannot not anticipate claims 1, 4-8, and 11, and this rejection under 35 U.S.C. §102(b) should be reversed.

d) Claims 1, 5, 6, and 11 over Kasiskie

The Final Office Action stated that claims 1, 5, 6, and 11 were rejected under 35 U.S.C.§102(b) as anticipated by Kasiskie, as evidenced by Wyne, for the reasons set forth in the Office Action mailed May 15, 2002.

The May 15, 2002 Office Action stated that Kasiskie teaches a method for treating patients diagnosed with a hyperlipidemia, involving administering to a patient an effective amount of lovastatin, and inhibitor of HMG-CoA reductase, to reduce the production of VLDL in the patient to reduce the level of VLDL in the plasma of the patient.

There is no evidence in Kasiskie that lovastatin acts to decrease plasma VLDL levels by reducing expression of apoE. As the Examiner acknowledged, lovastatin is an inhibitor of HMG-CoA reductase. Furthermore, as discussed above, Wyne states that HMG-CoA reductase is a rate-limiting enzyme in cholesterol synthesis and as such reduces the level of downstream products. Wyne does not disclose that mevinolin reduces apoE expression.

In view of the fact that Kasiskie does not disclose or suggest a method of reducing the plasma level of VLDL in a host, comprising administering an agent that reduces the amount of plasma active apoE by

reducing the expression of apoE, Kasiskie cannot not anticipate claims 1, 5, 6, and 11, and this rejection under 35 U.S.C. §102(b) should be reversed.

SUMMARY

The instant specification provides ample written description for the claimed invention. Appellants have provided a detailed list of at least three different classes of agents suitable for use in the present invention. Appellants' discovery that elevated apoE expression is associated with elevated plasma VLDL levels, coupled with the description in the specification and that which is known in the art, would reasonably convey to the skilled artisan that Appellants were in possession of the claimed invention as of the filing date. As such, the instant specification provides meets the written description requirements of 35 U.S.C.§112, first paragraph.

The instant specification provides ample enablement for the claimed invention such that one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. Practice of the claimed methods would not require undue experimentation because a) the sequence of an apoE gene is known; b) guidance is given on how to test whether a give agent reduces apoE gene expression to a level sufficient to reduce VLDL production; c) there is ample guidance in the art for how to make and use agents, such as antisense nucleic acids, that reduce apoE expression; and d) one of skill in the art would be able to perform, as a matter of routine, experiments to determine whether a given agent reduces apoE expression to the requisite degree. As such, the instant specification meets the enablement requirement of 35 U.S.C.§112, first paragraph.

The phrase "a disease condition associated with elevated plasma levels of VLDL" as recited in claims 5 and 11 is clear, given the disclosure of the specification. The specification discusses disorders, including Type IV hyperlipidemia and Type IIb hyperlipidemia, that are associated with elevated plasma VLDL levels. Furthermore, disorders associated with elevated plasma VLDL levels are known in the art. In view of the disclosure in the specification and the knowledge in the art regarding such disorders, the phrase "a disease condition associated with elevated plasma levels of VLDL" in claims 5 and 11 is clear. As such, claims 5 and 11 meet the requirements of 35 U.S.C.§112, second paragraph

None of the cited art, i.e., Ditschuneit, Yoshino, Connor, and Kasiskie, is properly cited as an anticipating reference, because none of the cited art discloses a method of reducing a plasma VLDL level in a host, comprising administering an effective amount of an agent that reduces the amount of plasma active poE by reducing the expression of apoE. None of the agents discussed – gemfibrozil, pravastatin, dietary n-3 fatty acids, and lovastatin – reduces apoE gene expression. Accordingly, none of the cited art anticipates the instant invention as claimed.

RELIEF REQUESTED

Appellants respectfully request that the rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, first paragraph; the rejection of claims 5 and 11 under 35 U.S.C.§112, second paragraph; and the rejection of claims 1, 4-8, and 11, and claims 1, 5, 6, and 11 under 35 U.S.C. §102(b) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,
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Date: April 25, 2003

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APPENDIX OF PENDING CLAIMS

1. (Previously Amended) A method for reducing the plasma level of VLDL in a host, said method comprising:

administering to said host an effective amount of an agent which reduces the amount of plasma active apoE in said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production in said host to reduce the plasma level of VLDL in said host, whereby the plasma level of VLDL in said host is reduced by at least two fold.

2-3. (Canceled)

4. (Original) The method according to Claim 1, wherein said apoE is apoE3.

5. (Previously Amended) A method of treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, said method comprising:

administering to said host an effective amount of an agent that reduces the plasma amount of active apoE in said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production by at least two fold to treat said disease condition, whereby said host is treated.

6. (Original) The method according to Claim 5, wherein said disease condition is a hyperlipidemia.

7. (Original) The method according to Claim 6, wherein said hyperlipidemia is Type IV hyperlipidemia.

8. (Original) The method according to Claim 6, wherein said hyperlipidemia is Type IIb hyperlipidemia.

9-10. (Canceled)

11. (Original) The method according to Claim 5, wherein said apoE is apoE3.

12-35. (Withdrawn)